4,5,6-Trisubstituted piperidinones as conformationally restricted ceramide analogues: synthesis and evaluation as inhibitors of sphingosine and ceramide kinases and as NKT cell-stimulatory antigens

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The conformationally based piperidinone sphingosine analogues 7, 8, 15, and 16 were synthesized from allylic alcohol 34 via lactams 31 and 32. The L-arabino diol 7 and the L-ribo diol 8 were transformed into the amino alcohols 17-24. The L-gluco ceramide analogues 43, 46a, and 47, and the L-altro ceramide analogues 51a and 52 were synthesized from either 31 or 32. The L-ribo diols 8 and 16, and the amino alcohols 19 and 20 inhibit sphingosine kinase 1 (SPHK1), while the L-arabino analogues 7, 15, 17, and 18 are inactive. The L-arabino and the L-ribo dimethylamines 21-24, the L-gluco ceramide analogues 43, 46a, and 47, and the L-altro ceramide analogues 51a and 52 did not block SPHK1. Neither the L-arabino diol 7 nor the L-ribo diol 8 inhibited SPHK2 or ceramide kinase. The L-arabino diols 7 and 15 stimulate invariant natural killer T (iNKT) cells when presented by living antigen-presenting cells (APC) and also by plate-bound human CD1d, whereas the L-ribo diols 8 and 16, the L-arabino amino alcohols 17-18, and the dimethylamines 21-22 did not activate iNKT cells. The L-gluco ceramide analogues 43, 46a, and 47 had strongly stimulatory effects on iNKT cells when presented by living APC and also by plate-bound human CD1d, whereas the L-altro ceramide analogue 52 activated only weakly. All activatory compounds induced preferentially the release of pro-inflammatory cytokines, indicating the formation of a stable CD1d–lipid–T-cell receptor complex.
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